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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/023,232	02/13/98	MONOSOV	A	312762001530

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THOMAS D MAYS
MORRISON & FOERSTER
2000 PENNSYLVANIA AVENUE NW
WASHINGTON DC 20006-1888

EXAMINER	
BECKERLEG,A	
ART UNIT	**PAPER NUMBER**
1632	9

DATE MAILED: 10/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 09/023,232	Applicant(s) Monosov et al.
	Examiner Anne Marie S. Beckerleg	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-29* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-29* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Reissue Applications

This reissue application was filed without the required offer to surrender the original patent or, if the original is lost or inaccessible, an affidavit or declaration to that effect. The original patent, or an affidavit or declaration as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.

Oath/Declaration

Applicant's petition under 37 CFR 1.47(b) filed January 18, 2000, which is being treated as a petition under 37 CFR 1.183 requesting waiver of 37 CFR 1.67 and 1.172 which would require that the supplemental reissue declaration of January 18, 2000 have been executed by the inventors has been granted. A notice to that effect was mailed to the applicant's representatives on 9/19/2000. Therefore, the supplemental reissue application declaration and power of attorney signed by the sole assignee of interest, Anticancer, Inc., is accepted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19, 26, and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nude or immunodeficient rodent models for human neoplastic disease, does not reasonably provide enablement for the use of any and all non-human mammals as models for human cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

At the time of filing, the art reports several genetically immunodeficient rodents which lack T cells, including athymic nude mice and rats, and SCID mice. Neither the prior art nor the specification teaches genetically immunodeficient non-human mammals other than rodents. Also, the specification does not provide guidance for making genetically immunodeficient mammals that are not rodents, or provide guidance for generating immunodeficiency in mammals such as porcupines or goats using any methodology. Further, the specification does not provide guidance as to the level of immunodeficiency that is "sufficient" to allow growth of human tumors in mammals other than rodents that mimics that observed in human patients, or provide working

examples demonstrating that any and all mammals other than rodents can be used as models for human neoplastic disease.

Therefore, based on the lack of known immunodeficient mammals other than rodents at the time of filing, the lack of guidance in the specification for making and using immunodeficient mammals other than rodents, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to make or use the scope of the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The applicant's claims recite the term "characterized by". A characterization is subjective and as such does not clearly point out the invention. It is suggested that the applicant replace "characterized by " with "has".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13, 15, 17, 19-20, 33, 35, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (1982) Exp. Cell. Biol., Vol. 50, 330-331 in view of McLemore et al. (1987) Cancer Research, Vol. 47(19), 5132-5140 in view of Otto et al. (1985) J. Urol., Vol. 134, 170-174. The applicant claims nude mouse, nude rodent, immunodeficient rodent, or non-human mammal models of human neoplastic disease characterized by having intact human neoplastic tissue of at least $1mm^3$ transplanted orthotopically, and having sufficient immuno-deficiency to allow said tissue to grow and mimic the progression of the neoplastic disease in the human donor, wherein said tissue is selected from breast, ovarian or lung (pleural) tissue, and methods of generating said models comprising orthotopic transplantation of said tissue. The applicant is reminded that, "[e]ven though product - by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product - by - process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe , 227 USPQ 964, 966 (Fed. Cir. 1985). MPEP 2113.

Wang et al. teaches the orthotopic transplantation of colonic tumors, maintained in nude mice, into the colonic wall of naive nude mice resulting in growth and metastasis of the colonic tumors which mimic the pattern observed in the original human patients (Wang et al., page 331,

abstract). McLemore et al. teaches an athymic nude mouse model for human lung cancer, wherein nude mice receive orthotopic transplantation of several different human lung carcinoma cells lines intrabronchially (McLemore et al., page 5133, column 2 paragraphs 2-4). McLemore et al. further provides motivation for using orthotopic transplantation versus subcutaneous transplantation of human tumors in nude mice by demonstrating that mice transplanted intrabronchially with lung tumor cells demonstrated increased rates of growth and metastases than those transplanted subcutaneously (McLemore et al., page 5132, abstract, and 5133, Table 1).

Wang et al. does not specifically disclose the condition of the colonic tumors transplanted into the nude mice. McLemore et al. teaches the transplantation of cell suspensions. Thus, neither Wang nor McLemore specifically teach the transplantation of intact fragments of human tumors. Otto et al. supplements Wang et al. and McLemore et al. by teaching the direct transplantation of human renal cell carcinoma embedded in renal tissue to nude mice from nephrectomized patients (Protocol I), and by teaching the direct transplantation of human tumor tissue grown in mice to other naive nude mice (Protocol II) (Otto et al., page 170, column 1, paragraphs 3-4, and column 2, paragraphs 1-2). Otto et al. also teaches that the growth of tumor tissue transplanted directly from the patients correlated well with the clinical course of the patients (Otto et al., page 170, column 2, paragraph 5). Based on the teachings of Otto et al., that human neoplastic tissue can be transplanted directly from patients to nude mice and that the growth and morphology of the neoplastic tissue resembles that seen in the patient, the skilled artisan would have been motivated to transplant human neoplastic tissue rather than human neoplastic cells in suspension in order to

save the time and effort of generating and maintaining human cell lines *in vitro* that retain the characteristics of the original tumor.

Thus, in view of the benefits of using neoplastic tissue over a cell suspension as provided by Otto et al., it would have been *prima facie o*bvious to the skilled artisan to substitute intact tumor tissue for the tumor or cells taught by Wang et al. or McLemore et al. in the method of generating a nude mouse model of human cancer by orthotopic transplantation as taught by Wang et al. Furthermore, based on the teachings of Otto et al. that intact tumor tissue maintains growth and morphological characteristics in the nude mouse, and the teachings of Wang et al. and McLemore et al. that orthotopic transplantation in nude mice versus subcutaneous transplantation more closely mimics the growth and metastases of human tumors in patients, the skilled artisan would have had a reasonable expectation of success in generating and using a nude mouse model for human neoplastic disease characterized by orthotopically transplanted intact colon or lung tissue. In addition, as the art of record teaches that many different types of tumor tissue, including colonic, lung, and renal tissue, can be transplanted orthotopically into mice to generate a mouse model for human neoplastic disease, it would have been *prima facie* obvious to the skilled artisan to generate a nude mouse model for any type of human cancer, including breast or ovarian cancer, by implanting the human neoplastic tissue into the analogous murine tissue. Therefore, in view of the high level of surgical skill in transplanting tissue into mice at the time of filing, the motivation to generate mouse models for many different kinds of human tumors by orthotopically transplanting human tumor tissue to nude or immunodeficient mice as provided by Wang et al.,

McLemore et al., and Otto et al., the skilled artisan would have had a reasonable expectation of success in implanting neoplastic human breast or ovarian tissue into murine breast or ovarian tissue respectively in order to produce a murine model for human breast or ovarian neoplastic disease.

Claims 14, 16, 21, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over McLemore et al. (1987) Cancer Research, Vol. 47, 5132-5140 in view of Otto et al. (1985) J. Urol., Vol. 134, 170-174 as applied to claims 1-17, 24, 26, 28-29, 31, 33, and 35-38 above, and further in view of Giovanella et al. (1984) Exp. Cell. Biol., Vol. 52, 76-79. The applicant claims a nude or immunodeficient rat model for human neoplastic disease characterized by having intact human neoplastic tissue of at least $1mm^3$ transplanted orthotopically and having sufficient immuno-deficiency to allow said tissue to grow and mimic the progression of the neoplastic disease in the human donor, and methods of generating said models comprising orthotopic transplantation of said tissue.

As discussed in the preceding rejection, the combined teachings of Wang et al. in view of McLemore et al. in view of Otto et al. provide the methods and motivation for making and using a nude mouse model for human cancer comprising the orthotopic transplantation of intact human colon or lung tissue. Wang, McLemore, and Otto all teach nude mouse models. Giovanella et al. teaches that human tumors can be transplanted and grown in either nude mice or rats (Giovanella et al., page 76, Tables I and II). Giovanella et al. also teaches that human tumors grow more

rapidly in nude rats than in nude mice (Giovanella et al., page 77 Figures 1-2). Thus, it would have been *prima facie* obvious to the skilled artisan to substitute nude rats for nude mice in a nude rodent model for human neoplastic disease in order to decrease the time required to conduct experiments. Further, based on the teachings of Giovanella et al., that human tumors grow in rats, the skilled artisan would have had a reasonable expectation of success in using a nude rat to generate a model for human cancer comprising the orthotopic transplantation of intact tumor tissue.

Claims 18 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over as applied to claims 1-17, 24, 26, 28-29, 31, 33, and 35-38 above, and further in view of Reddy et al. (1987) Cancer Res., Vol. 47 (9), 2456-2460. The applicant claims an immunodeficient SCID mouse model for human neoplastic disease characterized by having intact human neoplastic tissue of at least $1mm^3$ transplanted orthotopically and having sufficient immuno-deficiency to allow said tissue to grow and mimic the progression of the neoplastic disease in the human, and methods of generating said model comprising orthotopic transplantation of said tissue.

As discussed in the preceding rejection, the combined teachings of Wang et al. in view of McLemore et al. in view of Otto et al. provide the methods and motivation for making and using a nude mouse model for human cancer comprising the orthotopic transplantation of intact human colon or lung tissue. Wang, McLemore, and Otto all teach nude mouse models. Reddy et al. teaches a SCID mouse model of human lung cancer comprising the transplantation of human lung

tumor cells to SCID mice (Reddy et al., page 2456, abstract). Reddy et al. also provides motivation for substituting the SCID mouse for the nude mouse by teaching that 100% of the transplanted mice developed tumors, and that, " mice with this severe combined immunodeficiency represent a new and viable model for propagating human tumors and for evaluating the efficacy of novel drug delivery protocols in the treatment of cancer" (Reddy et al., abstract). Thus, based on the teachings of Reddy et al., it would have been *prima facie* obvious at the time of filing to substitute a SCID mouse for the nude mice taught by Wang, McLemore, and Otto, and the skilled artisan would have had a reasonable expectation of success in both generating and using a SCID mouse model for human neoplastic disease characterized by orthotopic transplantation of intact human tumor tissue.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 8:30-6:00. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Karen M. Hauda

KAREN M. HAUDA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600